Applicants respectfully point out that the term "third" does not relate to a location or position within a structure, but relates simply to the modification, *e.g.*, a disruption or deletion, of a third nucleic acid sequence encoding a protein that may be detrimental to the production, recovery, and/or application of the heterologous polypeptide of interest. On page 8, line 22, to page 9, line 4, of the specification, a third nucleic acid sequence is defined by Applicants. The specification states: "In another aspect of the present invention, the mutant filamentous fungal cell may additionally contain modifications of one or more third nucleic acid sequences that encode proteins that may be detrimental to the production, recovery, and/or application of the heterologous polypeptide of interest. The modification reduces or eliminates expression of the one or more third nucleic acid sequences resulting in a mutant cell that may produce more of the heterologous polypeptide than the mutant cell without the modification of the third nucleic acid sequence when cultured under the same conditions. The third nucleic acid sequence may encode any protein or enzyme. For example, the enzyme may be an aminopeptidase, amylase, carbohydrase, carboxypeptidase, catalase, cellulase, chitinase, cutinase, cyclodextrin glycosyltransferase, deoxyribonuclease, esterase, alpha-galactosidase, beta-galactosidase, glucoamylase, alpha-glucosidase, beta-glucosidase, invertase, laccase, lipase, mannosidase, mutanase, oxidase, pectinolytic enzyme, peroxidase, phospholipase, phytase, polyphenoloxidase, proteolytic enzyme, ribonuclease, transglutaminase, or xylanase. The third nucleic acid sequence preferably encodes a proteolytic enzyme, *e.g.*, an aminopeptidase, carboxypeptidase, or endoprotease." Moreover, the claim recites "the mutant cell <u>further</u> comprises one or more modifications of one or more third nucleic acid sequences." The term "further" means in addition to the first and second nucleic acid sequences, not in place of first and second nucleic acid sequences. Applicants assert, therefore, that the term "third" is not vague and indefinite.

For the foregoing reason, Applicants submit that the rejection under 35 U.S.C. § 112, second paragraph, has been overcome and respectfully request reconsideration and withdrawal of the rejection.

II. Rejection of Claims 70-71, 82-90, 91, and 97 under 35 U.S.C. § 112, First Paragraph

Claims 70-71, 82-90, 91, and 97 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action specifically states:

> Claims 70-71, 82-90, 91 and 97 are drawn to any filamentous fungal cell modified in any way so that said cell is deficient in the production of cyclohexadepsipeptides, and

> a method of producing secreted heterologous proteins in such host cell. The specification discloses the construction of mutant *Fusarium venenatum* host cells wherein the *esyn1* gene, which codes for enniatin synthetase, and the *dps1* gene, which codes for a cyclohexadepsipeptide synthetase, were disrupted (pages 31-38). The specification also discloses the sequences of the *Fusarium venenatum* cyclohexadepsipeptide synthetase and its corresponding polynucleotide (page 27-page 28, line 2). ... In the instant case, only two gene modifications have been located in one filamentous fungal host cell that resulted in deficient production of cyclohexadepsipeptide, which is insufficient to put one of skill in the art in possession of the attributes and features of any mutant filamentous fungal cells deficient in cyclohexadepsipeptide production and methods of using said cells in the production of secreted cells.

This rejection is respectfully traversed.

The Office Action indicates that "only two gene modifications have been located in one filamentous fungal host cell that resulted in deficient production of cyclohexadepsipeptide, which is insufficient to put one of skill in the art in possession of the attributes and features of any mutant filamentous fungal cells deficient in cyclohexadepsipeptide production and methods of using said cells in the production of secreted cells." Applicants respectfully disagree.

Applicants have described how to produce mutant cells in filamentous fungi by deleting or disrupting nucleic acid sequences encoding cyclohexadepsipeptide synthetases in filamentous fungal cells (see page 5, line 14 to page 8, line 3 and Examples 5 and 6) and how to express a secreted heterologous protein in such cells (page 11, line 22, to page 17, line 24). From page 5, line 14, to page 7, line 23, Applicants also disclose several other procedures well known in the art for modifying the production of cyclohexadepsipeptides in the filamentous fungal cells. While the Examples describe a *Fusarium* cell, with the information provided by the Applicants in the specification and the knowledge available in the pertinent art, one skilled in the art can construct disruption or deletion vectors for transformation into any filamentous fungal cell, shown to produce cyclohexadepsipeptide, to disrupt or delete a gene involved in the biosynthesis of cyclohexadepsipeptide. For example, by selecting a highly conserved region of the *Fusarium* gene of SEQ ID NO: 1 relative to other similar genes in the prior art, a disruption or deletion vector can be prepared without knowledge of the corresponding gene sequence in another filamentous fungal cell. It is reasonably predictable that such a conserved region will be relatively homologous with similar genes from other filamentous fungi.

A DNA fragment containing the conserved region interrupted with a selectable marker or a DNA fragment with a portion of the conserved region removed by digestion with a restriction enzyme can, therefore, be used with reasonable predictability to replace the corresponding similar gene via homologous recombination in any filamentous fungal cell that produces cyclohexdepsipeptide. In fact,

Herrmann *et al.* (*Molecular Plant-Microbe Interactions* 9: 226-232, 1996) have shown that an internal fragment of the *Fusarium scirpi esyn1* gene was useful in disrupting the *Fusarium avenaceum* enniatin synthetase gene without any knowledge of the nucleic acid sequence of the *Fusarium avenaceum* gene. Thus, the need for isolation of the genes, delineation of the nucleic acid sequences, and a determination of which modifications would lead to deficient production of cyclohexadepsipeptides is not necessary to disrupt or delete a gene involved in the biosynthesis of cyclohexadepsipeptide. As page 5, line 14 to page 7, line 23, of the Applicants specification indicates, a deletion or disruption of a gene is sufficient to eliminate production of cyclohexadepsipeptides.

Applicants assert, therefore, that at the time the application was filed, Applicants had possession of the claimed invention because the claims are supported by Applicants' written description. The specification provides sufficient information to one of ordinary skill in the art to make cyclohexadepsipeptide-deficient cells in filamentous fungi other than *Fusarium* using the nucleic acid sequences disclosed in the specification and the prior art without being provided with the corresponding DNA sequences encoding the enzymes involved in the biosynthesis of cyclohexadepsipeptide. However, to further prosecution of the instant application, the claims now recite "*Fusarium* cell" in place of "filamentous fungal cell."

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome and respectfully request reconsideration and withdrawal of the rejections.

III. Rejection of Claims 70-71, 82-90, 91, and 97 under 35 U.S.C. 112, first paragraph

Claims 70-71, 82-90, 91 and 97 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Office Action states:

> The specification, while being enabling for a mutant *Fusarium* cell and a method of use of said cell to produce secreted proteins, wherein the *Fusarium* cell comprises disruptions in the enniatin synthetase gene and the cyclohexadepsipeptide synthetase gene such that the *Fusarium* cell is deficient in the production of cyclohexadepsipeptides, does not reasonably provide enablement for <u>any mutant filamentous fungal host cell</u> and a method of use of such cell to produce secreted proteins, wherein the filamentous fungal contains <u>any modification</u> such that the filamentous fungal cell is deficient in the production of cyclohexadepsipeptide.

This rejection is respectfully traversed.

The Office Action asserts that "[t]he specification, while being enabling for a mutant *Fusarium*

cell and a method of use of said cell to produce secreted proteins does not reasonably provide enablement for any mutant filamentous fungal host cell. Applicants respectfully disagree with this contention.

Applicants have provided an enabling disclosure on how to produce mutant cells by disrupting or deleting nucleic acid sequences encoding cyclohexadepsipeptide synthetases in filamentous fungal cells (see page 5, line 14 to page 8, line 3 and Examples 5 and 6) and how to express a secreted heterologous protein in such cells (page 11, line 22, to page 17, line 24). As noted in Section II, based on the information provided by the Applicants in the specification and the knowledge available in the pertinent art, one skilled in the art can construct disruption or deletion vectors for transformation into any filamentous fungal cell, shown to produce cyclohexadepsipeptide, to disrupt or delete a gene involved in the biosynthesis of cyclohexadepsipeptide. For example, as noted above, by selecting a highly conserved region of the *Fusarium* gene of SEQ ID NO: 1 relative to other similar genes in the prior art, a deletion vector can be prepared without knowledge of the corresponding gene sequence in another filamentous fungal cell. It is reasonably predictable that such a conserved region will be relatively homologous with similar genes from other filamentous fungi. Thus, a DNA fragment containing the conserved region interrupted with a selectable marker or a DNA fragment with a portion of the conserved region removed by digestion with a restriction enzyme can be used with reasonable predictability to replace the corresponding similar gene via homologous recombination in any filamentous fungal cell that produces cyclohexdepsipeptide.

Applicants have shown that the deduced amino acid sequence (SEQ ID NO:2) of the cyclohexadepsipeptide synthetase gene (SEQ ID NO:1) shares approximately 59% identity with the enniatin synthetase of *Fusarium scirpi* (Haese *et al.*, 1993, *Mol. Microbiol.* 7: 905-914; DNA sequence listed in EMBL database under accession number Z18755). This sequence comparison indicates there are regions of conserved homology between the sequences at the DNA level, which can be used to construct a disruption or deletion vector for use in another filamentous fungus without any knowledge of the DNA sequence in that filamentous fungus. In fact, Herrmann *et al.* (*Molecular Plant-Microbe Interactions* 9: 226-232, 1996) have shown that an internal fragment of the *Fusarium scirpi esyn1* gene was useful in disrupting the *Fusarium avenaceum* enniatin synthetase gene without any knowledge of the nucleic acid sequence of the *Fusarium avenaceum* gene.

Applicants have also shown that the production of cyclohexadepsipeptides have been reported by *Polyporus* (Deol *et al.*, 1978, *Aust. J. Chem.* 31: 1397-1399) and *Alternaria* (McKee *et al.*, 1997, *Journal of Natural Products* 60: 431-438), both filamentous fungi. While genes encoding cyclohexadepsipeptides have not yet been isolated from *Polyporus* and *Alternaria*, the need for

isolation of the genes and delineation of the nucleic acid sequences is not necessary to disrupt or delete a gene involved in the biosynthesis of cyclohexadepsipeptide, as described above.

Applicants assert, therefore, that it is well within the skill of the art to make cyclohexadepsipeptide-deficient cells in filamentous fungi other than *Fusarium* using the nucleic acid sequences disclosed in the specification and the prior art without being provided with the corresponding DNA sequences encoding the enzymes involved in the biosynthesis of cyclohexadepsipeptide. However, as mentioned above, to further prosecution of the instant application, the claims now recite "*Fusarium* cell" in place of "filamentous fungal cell."

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome and respectfully request reconsideration and withdrawal of the rejections.

IV. Rejection of Claims 72-76 under 35 U.S.C. § 112, first paragraph

Claims 72-76 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action states:

> To adequately describe the claimed genera of modifications, one would require knowledge of which modifications would lead to disruption in the production of cyclohexadepsipeptides in the *Fusarium* cells claimed such that they can be used in the claimed method. In the instant case, only two gene modifications have been disclosed in one filamentous fungal host cell that resulted in deficient production of cyclohexadepsipeptides, which is insufficient to put one of skill in the art in possession of the attributes and features of mutant *Fusarium* cells deficient in cyclohexadepsipeptide production and methods of using said cells in the production of secreted proteins. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant invention was filed.

This rejection is respectfully traversed.

The Office Action suggests that Applicants have not provided sufficient knowledge of which modifications would lead to disruption in the production of cyclohexadepsipeptides in the *Fusarium* cells to adequately describe the genera of modifications. Applicants respectfully disagree with this contention.

Applicants disclose several procedures well known in the art for modifying the production of cyclohexadepsipeptides in *Fusarium* cells on page 5, line 14 to page 7, line 23, of the specification. In particular, the techniques of gene disruption or gene deletion are preferred techniques in the methods

of the present invention. Applicants describe in Example 5 the construction of a deletion vector for deleting a portion of the *dps1* gene. However, it is well within the skill in the art to use any of the procedures described by the Applicants. Based on Applicants' specification and the knowledge available in the pertinent art, one skilled in the art can construct disruption or deletion vectors for transformation into any *Fusarium* cell, shown to produce cyclohexadepsipeptide, to disrupt or delete partially a gene involved in the biosynthesis of cyclohexadepsipeptide. By selecting a highly conserved region of the *Fusarium* gene of SEQ ID NO: 1 relative to other similar genes in the prior art, a deletion vector can be prepared without knowledge of the corresponding gene sequence in another filamentous fungal cell (see Section II). It is reasonably predictable that such a conserved region will be relatively homologous with similar genes from other *Fusarium* strains. Applicants submit that it is well within the skill in the art in conjunction with Applicants' specification to disrupt the production of cyclohexadepsipeptides in *Fusarium* cells.

Applicants assert, therefore, that at the time the application was filed, Applicants had possession of the claimed invention because the claims are supported by Applicants' written description.

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome and respectfully request reconsideration and withdrawal of the rejections.

V. Rejection of Claims 72-76 under 35 U.S.C. § 112, First Paragraph

Claims 72-76 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Office Action states:

> [T[he specification, while being enabling for a mutant *Fusarium* cell and a method of use of said cell to produce secreted proteins, wherein the *Fusarium* cell comprises disruptions in the enniatin synthetase gene and the cyclohexadepsipeptide synthetase gene such that the *Fusarium* cell is deficient in the production of cyclohexadepsipeptides, does not reasonably provide enablement for mutant *Fusarium* cells and a method of use of such cell to produce secreted proteins, wherein the *Fusarium* cells contain <u>any modification</u> such that the *Fusarium* cell is deficient in the production of cyclohexadepsipeptides.

This rejection is respectfully traversed.

The Office Action asserts that "due to the lack of relevant examples, the amount of information provided, and the lack of knowledge about which critical structural elements should be modified to

reduce or eliminate production of cyclohexadepsipeptides, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to determine which modifications in a *Fusarium* cell would lead to deficient production of cyclohexadepsipeptides." Applicants respectfully disagree with this assertion.

As noted in Section III, Applicants have provided an enabling disclosure on how to produce mutant filamentous fungal cells by deleting or disrupting nucleic acid sequences encoding cyclohexadepsipeptide synthetases in *Fusarium* cells (see page 5, line 14 to page 8, line 3 and Examples 5 and 6) and how to express a heterologous protein in such cells (page 11, line 22, to page 17, line 24). In addition to the arguments presented in Section III, Applicants disclose other genes on page 7, line 27, to page 8, line 3, which can be used in the methods of the present invention such as *Fusarium scirpi* as a source for an enniatin synthetase gene and *Fusarium sambucinum*as as a source for a D-hydroxyisovalerate dehydrogenase gene. Knowledge about which critical structural elements which should be modified to reduce or eliminate production of cyclohexadepsipeptides is unnecessary because by selecting a highly conserved region of a particular *Fusarium* gene relative to other similar genes in the prior art, a deletion vector can be prepared without knowledge of the corresponding gene sequence in another *Fusarium* cell. Applicants are simply disrupting a gene sequence or removing a portion of the gene sequence so expression of the gene is disrupted and no cyclohexadepsipeptide is produced. For example, Herrmann *et al.* (*Molecular Plant-Microbe Interactions* 9: 226-232, 1996) have shown that an internal fragment of the *Fusarium scirpi esyn1* gene was useful in disrupting the *Fusarium avenaceum* enniatin synthetase gene without any knowledge of the nucleic acid sequence of the *Fusarium avenaceum* gene.

Applicants assert, therefore, that it is well within the skill of the art to make cyclohexadepsipeptide-deficient *Fusarium* cells using the nucleic acid sequences disclosed in the specification and the prior art without being provided with the DNA sequences encoding the enzymes involved in the biosynthesis of cyclohexadepsipeptide.

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome and respectfully request reconsideration and withdrawal of the rejections.

VI. Rejection of Claims 77-81 and 92-96 under 35 U.S.C. § 112, First Paragraph

Claims 77-81 and 92-96 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession

of the claimed. The Office Action states:

> To adequately describe the claimed genera of mutant filamentous fungal cells, one would require some knowledge of the gene structure and which modifications would be required in such genes to obtain cells deficient in the production of cyclohexadepsipeptides. In the absence of this information, one cannot construct such mutant cells and therefore, cannot use such cells in the claimed method. In the instant case, only two gene structures and modifications have been disclosed for one filamentous fungal host cell (*Fusarium*) that resulted in deficient production of cyclohexadepsipeptides, which is insufficient to put one of skill in the art in possession of the attributes and features of any filamentous fungal cell comprising mutations in the cyclohexadepsipeptide synthetase gene, enniatin synthetase gene, or the D-hydroxyisovalerate dehydrogenase gene and methods of using said cells in the production of secreted proteins. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

This rejection is respectfully traversed.

For the same reasons explained in Sections II and IV (see above), Applicants assert that the subject matter is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome and respectfully request reconsideration and withdrawal of the rejections.

VII. Rejection of Claims 77-81 and 92-96 under 35 U.S.C. § 112, First Paragraph

Claims 77-81 and 92-96 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Office Action states:

> [T]he specification, while being enabling for a mutant *Fusarium* cell and a method of use of said cell to produce secreted proteins, wherein the *Fusarium* cell comprises disruptions in the enniatin synthetase gene and the cyclohexadepsipeptide synthethase gene such that the *Fusarium* cell is deficient in the production of cyclohexadepsipeptides, does not reasonably provide enablement for <u>any mutant filamentous fungal host cell</u> and a method of use of such cell to produce secreted proteins, wherein the filamentous fungal cell contains mutations in the cyclohexadepsipeptide synthetase gene, enniatin synthetase gene, or the D-hydroxyisovalerate dehydrogenase gene, such that the filamentous fungal cell is deficient in the production of cyclohexadepsipeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is respectfully traversed.

For the same reasons explained in sections III and V (see above), Applicants assert that the specification does enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome and respectfully request reconsideration and withdrawal of the rejections.

VIII. Rejection of Claims 70-72, 77-78, 80, 86-87, 91-93, and 95 under 35 U.S.C. § 103

Claims 70-72, 77-78, 80, 86-87, 91-93, and 95 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over by Herrmann *et al.* (*Molecular Plant-Microbe Interactions* 9: 226-232, 1996) in view of Tsuchiya *et al.* (*Appl. Microbial. Biotechnol.* 40: 327-332, 1993). The Office Action states:

> Herrmann *et al.* teaches the construction of a mutant *Fusarium* cell which produces less cyclohexadepsipeptide due to the disruption of the enniatin synthetase gene (pages 230-231, Materials and Methods). Herrmann *et al.* does not teach a method for producing a secreted heterologous protein. Tsuchiya et al. teaches the expression of secreted calf chymosin in the filamentous fungus *Aspergillus oryzae* (page 327, Abstract). Tsuchiya *et al.* does not teach a filamentous fungal cell which produces less cyclohexadepsipeptide. ... It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the enniatin synthetase mutant filamentous fungal cell of Herrmann et al. to express secreted recombinant proteins such as the calf protease (chymosin) of Tsuchiya *et al.* for the benefit of secretion in a filamentous fungal cell such as *Fusarium*.

This rejection is respectfully traversed.

The Office Action asserts that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to use the enniatin synthetase mutant filamentous fungal cell of Herrmann *et al.* to express secreted recombinant proteins such as the calf protease (chymosin) of Tsuchiya *et al.* for the benefit of secretion in a filamentous fungal cell such as *Fusarium*." However, obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Applicant asserts that methods of producing a secreted heterologous polypeptide in a cyclohexadepsipeptide-deficient *Fusarium* cell would have not been obvious to one of ordinary skill in the art, based upon the teachings cited by the Office Action. None of the references, either alone or in combination, suggest or teach one of ordinary skill in the art methods of producing a secreted heterologous polypeptide in a cyclohexadepsipeptide-deficient *Fusarium* cell.

Herrmann *et al.* disclose the effect of disruption of the enniatin synthetase gene on the virulence of *Fusarium avenaceum*. The disruption of the enniatin synthetase gene was accomplished with a gene disruption plasmid that also contained the hygromycin B phosphotransferase gene from *E. coli* as a selection marker. However, Herrmann *et al.* do not disclose methods of producing a secreted heterologous polypeptide in a cyclohexadepsipeptide-deficient *Fusarium* cell, as claimed herein. Applicants' instant invention is directed to the production of secreted heterologous polypeptides, while Herrmann *et al.* disclose expression of hygromycin B phosphotransferase which is not a secreted enzyme.

Tsuchiya *et al.* disclose expression and secretion of calf chymosin from the filamentous fungus *Aspergillus oryzae*. However, Tsuchiya *et al.* do not disclose methods of producing a secreted heterologous polypeptide in a cyclohexadepsipeptide-deficient *Fusarium* cell, as claimed herein.

The Office Action states that "[a] person of ordinary skill in the art is motivated to use the mutant filamentous fungal cell of Herrmann *et al.* to produce secreted heterologous proteins because (1) secretion is advantageous due to faster recovery of the desired protein, (2) filamentous fungal cells are known to be good hosts for the production of recombinant proteins, and (3) the mutant cell of Herrmann *et al.* is not able to produce cyclohexadepsipeptides, which are known phytotoxins, therefore reducing the risk of isolating phytotoxins with the desired product."

The Office Action also states that "[o]ne of ordinary skill in the art has a reasonable expectation of success at being able to produce heterologous secreted proteins such as proteases, in the host of Herrmann *et al.* because transformation of filamentous fungal cells with a plasmid containing the DNA encoding the heterologous protein under the control of a promoter which would allow secretion is well known in the art and Tsuchiya *et al.* teach a method to secrete a heterologous protease in a filamentous fungal cell." Applicants disagree with this contention because neither Herrmann *et al.* nor Tsuchiya *et al.* teach or suggest that a cyclohexadepsipeptide-deficient *Fusarium* can be used as a host cell to produce a secreted heterologous polypeptide. Herrmann *et al.* teach a method for reducing the virulence of *Fusarium avenaceum*, but makes no mention of using such a strain for producing a secreted heterologous polypeptide. Tsuchiya *et al.* teach the use of an *Aspergillus oryzae* strain for expressing a foreign protein, but makes no mention of *Fusarium* strains for such a purpose. Even in combination, there is no suggestion that a cyclohexadepsipeptide-deficient *Fusarium* can be used as a host cell to produce a secreted heterologous polypeptide. Applicant asserts, therefore, that there is no motivation to combine the cited references

Applicant submits that hindsight reconstruction is involved in the Office Action's arguments. For prior art references to be combined to render obvious a subsequent invention under Section 103, there

must be something in the prior art as a whole which suggests the desirability, and thus the obviousness, of making the combination. *Uniroyal v. Rudkin-Wiley*, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988). It is impermissible to use the claims as a framework from which to pick and choose among individual references to recreate the claimed invention. *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

The references cited by the Examiner do not contain the requisite teaching, and therefore cannot be combined to support the obviousness rejections of the present claims. For the foregoing reason, Applicants submit that the rejections under 35 U.S.C. § 103(a) have been overcome and respectfully request reconsideration and withdrawal of the rejections.

IX. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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